evidence, applicants request the Examiner to withdraw the objection.

The Examiner has maintained the rejection of claims 3-5, 7, 10, 21 and 22 under 35 U.S.C. §§ 102 and 103 over European patent publication 382,526 ("EP 382,526") and United States patent 5,047,407. Applicants traverse.

Rejection over EP 382,526

EP 382,526 was published on August 16, 1990, more than three months after the effective priority date of this application. British priority application GB 9009861.7 (filed May 2, 1990) is identical in its disclosure to the pending application. A certified copy of the priority document was timely filed under the Patent Cooperation Treaty during the international stage of this application. No further documentation is necessary to perfect applicants' priority claim. Accordingly, EP 382,526 is not prior art and the rejections §§ 102 and 103 with respect to this document should be withdrawn.

§ 103 Rejection over U.S. Patent 5,047,407

Claims 3-5, 7, 10, and 21-22 stand rejected under § 103. The Examiner contends that the claimed (-)-enantiomer is obvious over the racemate disclosed in the commonly owned '407 patent. The Examiner suggests that the March 11, 1994 Declaration of Richard Storer which addresses the unexpected and superior properties of the claimed enantiomer is not persuasive. The Examiner asserts the following:

(1) The claimed compound is not a nucleoside and is "significantly more different from natural nucleoside[s]" than AZT, DDC and DDI. As a result, the Examiner implies that Dr.

Storer's comparison of the activity profile of the claimed nucleoside analogue with that of natural nucleosides and AZT, DDI and DDC is inappropriate.

(2) DeClercq shows that "(-)-carbovir is as active as (+)-carbovir, but is significantly less toxic. This evidences that activity and toxicity is [sic] not always go hand in hand." On the basis of this assertion, the Examiner disputes Dr. Storer's statements that those of skill in the art believed that "as a general rule the 'nonnatural' enantiomers do not possess significant antiviral activity" and that "antiviral activity and cytotoxicity went hand in hand."

(3) The Examiner states that the only way to overcome the § 103 rejection is to show that the superior property is unexpected and is not possessed by the prior art compound (racemic *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one). The Examiner the asserts that the specification compares only the (+) and the (-) enantiomers of *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one and that applicants have not provided a comparison with the racemate.

The Examiner's reading of the Storer Declaration, the DeClercq article, and the specification are flawed. As a consequence, the Examiner's conclusion that the claimed enantiomer is obvious is faulty and should be reconsidered and withdrawn.

The Examiner's assertion that the claimed enantiomer cannot be meaningfully compared with natural nucleosides, AZT, DDI, and DDC is incorrect. Presumably, the Examiner believes that the heteroatom substitution on the sugar ring of the claimed compound prevented those of skill in the art in May 1990 from classifying and analyzing the compound as a "nucleoside

analog," like AZT, DDI and DDC. The Examiner's opinion is contrary to the evidence submitted by applicants and the Examiner's own statements about carbovir.

Applicants provided evidence in the Declaration of Dr. Richard Storer that *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one was considered to be a nucleoside analog in May 1990, the effective filing date of this application. The declaration establishes Dr. Storer as one of skill in the art of antiviral nucleoside chemistry at that date. (Dr. Storer has been a research chemist since 1973. From 1984 to 1993, he was actively involved in the antiviral chemistry and authored or co-authored fifty publications in this area, many describing work with antiviral nucleosides. (Decl. ¶ 2)) The Examiner has not challenged Dr. Storer's competence to provide evidence as to how those of skill in the art would have characterized the claimed compound or what they would have expected of its antiviral properties at the effective filing date of this application. Nor has the Examiner articulated any reasons or produced any evidence to contradict what Dr. Storer has stated (with the exception of a reference to carbovir which will be discussed below).

Dr. Storer stated that (-)-*cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one "belongs to a class of antiviral compounds known as 'nucleoside analogues.'" As a nucleoside analogue, Dr. Storer stated that he and those skilled in the art would have expected *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one to follow the molecular mimicry mechanism of action. Specifically, Dr. Storer stated that he and those skilled in the art would have believed that the enantiomer most closely resembling the native nucleoside, i.e., the "natural" enantiomer, would be the

active enantiomer and that the "nonnatural" enantiomer would have little or no activity. Dr. Storer concluded that the potent antiviral activity of (-)-*cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one (the "nonnatural" enantiomer) was surprising and unexpected. The Examiner has not challenged this conclusion and, in fact, has conceded as much. See August 9, 1994 Office Action, page 3: "The finding of nonnatural (-)-enantiomer is as active as the natural (+)-enantiomer is surprising."

Dr. Storer also stated that in view of the almost equivalent antiviral activity of the (+) and (-) enantiomers of *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one, those of skill in the art in May 1990 would not have expected the claimed (-) enantiomer to exhibit significantly less toxicity than the (+) enantiomer. ("Before that invention, we had believed that antiviral activity and cytotoxicity went hand in hand." (¶ 8))

The Examiner has not articulated any reasons or adduced any credible evidence to contradict Dr. Storer's testimony. However, to further support this testimony, applicants submit the Declarations of Dr. Mark Wainberg and Dr. Leroy Townsend. Both Dr. Wainberg and Dr. Townsend have extensive experience in the study of nucleoside analogs. Both believe that, at the effective filing date of this application, those of skill in the art would have expected the enantiomers of *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one to follow the activity pattern of other known nucleosides, i.e., that the "natural" enantiomer would be active and the "nonnatural" enantiomer relatively inactive. Both Drs. Wainberg and Townsend were surprised at the disclosed properties of the claimed compound and believe that others of skill in the

art at the effective filing date of this application were also surprised.

In view of the evidence provided by Dr. Storer, Dr. Townsend and Dr. Wainberg, and further in view of the Examiner's own comments with regard to carbovir (a nucleoside analog which also contains a substitution in the sugar ring and, as demonstrated below, exhibits properties consistent with those described as "expected" by Drs. Storer, Townsend and Wainberg), the Examiner should agree that those of skill in the art in May 1990 expected the enantiomers of *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one to follow the same activity and toxicity pattern as known nucleoside analogs and thus, the unexpected and superior properties of the claimed compound make it unobvious over the prior art.

With respect to the Examiner's assertion that the "results" reported in the DeClercq article refute Dr. Storer's evidence, applicants traverse. The Examiner's analysis of DeClercq is flawed for two reasons.

First, DeClercq was published in 1992, two years <u>after</u> the effective filing date of this application. Thus, nothing in DeClercq represents what was known or believed by those of skill in the art at applicants' filing date.

Second, DeClercq does <u>not</u> demonstrate that "(-)carbovir is as active as (+)carbovir but is significantly less toxic." DeClercq makes no reference whatsoever to (+) carbovir. Table 1 at page 122 provides data from prior publications pertaining to (-) carbovir and (±) carbovir (i.e., the <u>racemate</u>). Furthermore, a review of the underlying references relied upon by DeClercq to support this data, (Vince

and Hua* and Vince and Brownell*) shows that (-)-carbovir is the natural enantiomer. (See e.g., Vince and Brownell, p. 915 "The absolute stereochemistry of (-) carbovir has recently been determined to be analogous to the natural β-D-2'3'-didehydro-2'-3'-dideoxyguanosine.") Thus, the carbovir story supports, rather than contradicts, applicants' evidence.

Furthermore, it is not possible to directly compare the antiviral activity and toxicity of one compound in MT-2 cells and a different compound in H9 cells as the Examiner has done with the data provided in DeClercq, Table 1, page 122. Even the same compound demonstrates very different antiviral activity and toxicity values in different cell lines. See, e.g., Vince and Brownell's comparison of the antiviral activity and toxicity of (+) and (-) carbovir in MT-2C cells and H9 cells:

> "(-)-Carbovir showed an EC_{50} at 0.32 μg/mL (antiviral effect) while the cell viability profile of the MT-2C cells incubated with increasing concentrations of compound revealed and IC_{50} (cytotoxic effect) at 135 μg/mL. Thus, (-) carbovir exhibited a therapeutic index of 422 in this assay system. Conversely, the (+) isomer of carbovir is relatively inactive with an EC_{50} >50μg/mL" (p. 914)

and

> [In H9 cells] (-) Carbovir showed and EC_{50} at 0.8 μM compared to >60μM for (+) carbovir.... Evaluation of the carbovir enantiomers in uninfected H9 cells revealed IC_{50} values of >2mM (the highest concentration tested)" (p. 915). [Therapeutic index of (-) carbovir = 2500.]

Thus, the Examiner's characterization of the data provided in DeClercq is totally inaccurate and cannot be used to contradict the evidence provided by Dr. Storer.

Finally, with respect to the Examiner's assertion that applicants have not provided a comparison of the claimed (-) enantiomer with the prior art racemate, the Examiner is again

---

* Copies enclosed.

wrong. The specification at page 28, Tables 1 and 2 demonstrates that the antiviral activity of the (+) and (-) enantiomers of *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one is almost equal. In view of the previously reported antiviral activity of the racemate, it is inconceivable that those of skill in the art would not fully expect the racemate to possess substantially the same antiviral activity as its two enantiomers. Thus, in view of the data provided, a comparison of the antiviral activity of the claimed (-) enantiomer and the racemate is not necessary.

However, more importantly, the specification at page 29, Table 3, does compare the cytotoxicity of (+), (-) and racemic *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one (BCH-189). The same comparison was presented in J.A.V. Coates et al., "The Separated Enantiomers of 2'-Deoxy-3'-Thiacytidine (BCH-189) Both Inhibit Human Immunodeficiency Virus Replication In Vitro," Antimicrobial Agents and Chemotherapy, 36(1), pp. 202-205 (1992)*:

> "In CEM cells, the ID_{50} of the (+)-enantiomer was 3.84 ± 0.26 μM, whereas that of the (-)-enantiomer was >363 ± 102 μM .... The cytotoxicity seen with the racemate (ID_{50} 10.73 ± 0.22 μM) could be reproduced by mixing the enantiomers in a 1:1 ratio ..." (page 204, col. 1).

Thus, the data presented in the application (and confirmed in Coates) demonstrate that the claimed (-) enantiomer does possess superior and unexpected (and thus, unobvious) properties over the prior art racemate.

In summary, the Examiner has not credibly explained why the evidence submitted by Dr. Storer does not establish the unobviousness of the claimed subject matter. Thus, in view of the Declaration of Dr. Richard Storer as well as the supporting

---

* Copy enclosed.

Declarations of Dr. Mark Wainberg and Dr. Leroy Townsend, the following evidence must be accepted by the Examiner:

1. In May 1990, those of skill in the art would have expected *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one to behave as other nucleoside analogs, irrespective of whether and how it differs from AZT, DDI and DDC.
2. In May 1990, those of skill in the art expected antiviral activity of nucleoside analogs to reside in the enantiomer most closely resembling the natural nucleoside. The non-natural enantiomer was expected to possess little or no antiviral activity.
3. In May 1990, those of skill in the art believed that antiviral activity and cytotoxicity went hand in hand and would not have expected a difference in cytotoxicity, in view of the essentially equal antiviral activity, of the (+) and (-) enantiomers of *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one.
4. Those of skill in the art were surprised by and could not have predicted the superior properties exhibited by the claimed compound.

Applicants request that the Examiner reconsider and withdraw the § 103 rejection over United States patent 5,047,407.

<u>§ 102 Rejection over U.S. Patent 5,047,407</u>

The Examiner states that claim 10 of the '407 patent embraces "four compounds (optical isomers) and mixtures of them." She concludes that the number of compounds in this genus is "sufficiently small to support a 102 rejection." Applicants disagree with the Examiner's factual assertion and her conclusion from it.

The genus defined by claim 10, the geometric and optical isomers of 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane and mixtures of those isomers, includes hundreds of compositions. For example, the genus includes 50:50 mixtures of (+)-cis and (+)-trans 2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane as well as 20:80 mixtures of (+) and (-) trans-2-hydroxymethyl-5-(cytosin-1'-yl)-1,3-oxathiolane. Neither the specification nor the claims of the '407 patent specifically identify the claimed (-) enantiomer or suggests any preference or advantage in choosing the claimed enantiomer (or, for that matter, any other species) from the genus of claim 10. Further, as demonstrated above, those of skill in the art in May 1990, with the '407 patent in hand, would not have been motivated to choose the presently claimed (-) enantiomer from the genus of claim 10 because this particular enantiomer would not have been expected to possess significant antiviral activity.

In re Sivaramakrishnan, 213 USPQ 441, cited by the Examiner is distinguishable from the present case. In Sivaramakrishnan, the subject matter in dispute, cadmium laurate, was specifically recited in the prior art document. That is not the case here, where the '407 patent never specifically recites or suggests any particular optical isomer or mixture of optical or geometric isomers from the genus of claim 10.

Likewise, In re Schaumann, 197 USPQ 5, cited by the Examiner is also distinguishable from the present facts. In Schaumann, the Court considered the prior art to disclose a "small recognizable class [encompassing the claimed subject matter] with common properties." In the present case, the genus recited in claim 10 of the '407 patent encompasses geometric

isomers with vastly different activity and toxicity profiles, optical isomers of those geometric isomers, which again exhibit different properties and finally, hundreds of different mixtures of those isomers (geometric and optical) each of which may possess a different activity and toxicity profile.

The Examiner asserts that racemic *cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one, upon administration to a recipient is capable of providing (-)-*cis*-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one and thus anticipates the pending claims. The Examiner has not provided any evidence to support her assertion. Both Dr. Storer and Dr. Wainberg address the Examiner's allegation in their declarations. Neither believe, based on their experience with antiviral nucleosides, that the optical resolution proposed by the Examiner is plausible.

In view of the actual size of the genus described in claim 10 of the '407 patent, the teaching in the art away from the claimed enantiomer, and the evidence provided by Dr. Wainberg and Dr. Townsend, the '407 patent does not anticipate the claims of the present application. Accordingly, applicants request the Examiner to withdraw the rejection under § 102.

Finally, the Examiner has objected to pending claims 3-5, stating that the "degree of purity (claims 3-5) does not render patentability." Applicants disagree. If increased purity of a compound provides an unexpected advantage (as it does here) the degree of purity does render a compound patentable. This is a basic tenet of pharmaceutical and biotechnology patent practice.

The Declaration of Dr. Storer demonstrates that a mixture of the (+) and (-) enantiomers of *cis*-4-amino-1-(2-

hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one wherein the (+) enantiomer is present in no more than 5% w/w would possess the surprising antiviral activity and superior therapeutic index of the pure (-) enantiomer. The Examiner has provided no evidence to refute this. Accordingly, the Examiner should withdraw the objection.

For all of the foregoing reasons, applicants believe that the claims are in condition for allowance and request that the Examiner withdraw all rejections and allow this application.

Respectfully submitted,

Leslie A McDonell

James F. Haley, Jr. (Reg. No. 27,794)
Leslie A. McDonell (Reg. No. 34,872)
Attorneys for Applicants
c/o Fish & Neave
1251 Avenue of Americas
New York, New York 10021
(212) 596-9000

I Hereby Certify that this Correspondence is being Deposited with the U.S. Postal Service as First Class Mail in an Envelope Addressed to: ASSISTANT COMMISSIONER FOR PATENTS WASHINGTON D.C. 20231, on

July 19, 1996

Thomas Quinones
Name of Person Signing

Thomas Quinones
Signature of Person Signing